

Research Progress on Drug Nanocrystal Delivery Systems

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Abstract. Drug nanocrystals are submicron crystalline particles composed of pure drugs. With their extremely high drug loading capacity, significant solubility improvement ability, and flexible drug delivery route adaptability, they have become one of the key technologies to solve the problem of difficult-to-dissolve drug delivery. This article introduces two main preparation methods for drug nanocrystals, top-down techniques and bottom-up techniques, as well as three different dimensions of delivery applications and the stability issues they face. Among them, the research focuses on three drug delivery strategies of nanocrystals: oral, injectable, and targeted delivery. Nanocrystals can significantly enhance the bioavailability of poorly water-soluble drugs via the oral route, reduce excipient-related toxicity and achieve sustained release in injectable formulations, and enable precise intervention at the lesion site in topical and targeted delivery. This article also discusses the specific challenges faced by nanocrystals in terms of Ostwald ripening, drug degradation, and polymorphic transformation. Looking ahead, drug nanocrystals will be deeply integrated with smart materials and novel delivery devices to achieve precise targeted therapy, while further overcoming the stability and quality control hurdles in large-scale production, thereby accelerating their clinical translation.

Keywords: Drug nanocrystals, Drug delivery, Bioavailability

1. Introduction

Drug nanocrystals are a key technology for solving the problem of difficult-to-dissolve drug delivery. This material is a colloidal drug particle dispersion system prepared by selecting suitable stabilizers. Apart from stabilizers, there are no other medicinal carriers. The size is usually in the range of 100-1000 nm, which gives it a very high specific surface area and is the physical basis for improving the solubility of poorly soluble drugs [1]. Macedo et al.'s study observed that after being made into nanocrystals and orally administered, the C_{max} (The maximum concentration of a drug in the blood or plasma after administration) and AUC (Area Under the Curve: The total drug exposure over time, representing the integral of the concentration-time curve) of emtricitinib increased by 4 times and 3 times, respectively. During this process, fluctuations caused by food absorption were also eliminated, which greatly demonstrates the unique advantages of nanocrystals in oral delivery [2]. Patel et al. also reported similar positive results, showing that docetaxel nanocrystals coated with red blood cell membranes can achieve an AUC of 8.6 to 10.1 times that of free drugs in a glioma mouse model, and their half-life has been extended by 3.9 to 6.0 times. This undoubtedly

confirms the potential of nanocrystals in the field of brain-targeted delivery [1]. At the local treatment level, Alnaim et al.'s study provides another perspective: the ability of acyclovir nanocrystals to penetrate the skin is 6.3 times that of conventional formulations, which has found a better way out for the local administration strategy of insoluble drugs [3].

This article aims to comprehensively review the application progress and key challenges faced by drug nanocrystals in the field of insoluble drug delivery. The article will follow the two process routes of top-down and bottom-up methods to explain the specific rules of different preparation strategies for regulating the size, crystal structure, and stability of nanocrystals; At the same time, based on typical cases of oral, injection, and local delivery, analyze the core mechanisms by which nanocrystals improve bioavailability, achieve long-term sustained release, and enhance skin penetration; At the same time, it will also focus on its physical and chemical stability issues, and explore in-depth solutions for stabilizer selection and process optimization. It aims to provide a systematic reference for the rational design and industrial development of nanocrystalline formulations.

2. Preparation method of drug nanocrystals

2.1. Bottom-up techniques

The bottom-up method, also known as the anti-solvent precipitation method. Its core idea is to first dissolve poorly soluble drugs into a good solvent, and then inject this solution into an anti-solvent that has been pre-stabilized. At this point, the solubility of the drug in the environment will sharply decrease, rapidly reaching a supersaturation state, and thus rapidly precipitating to form nanocrystals [4]. Due to its simple operation process and low requirements for equipment cost, this method is more suitable for small-scale research in the laboratory. However, the entire mixing process is not easy to achieve precise control, and the formation and subsequent growth of crystal nuclei are also difficult to regulate freely, which directly leads to uneven distribution of nanoparticle size and poor repeatability between batches, which are obvious defects of traditional precipitation methods [4]. At the same time, the intervention of organic solvents not only poses a hidden danger of solvent residue but also means that drugs must be soluble in at least one type of organic solvent, which lowers the universality of the method [1].

In order to improve the above situation, many research teams have turned their attention to the development of microfluidic technology. For example, Shen et al. greatly improved the control ability of the crystallization process by achieving fast and uniform mixed mass transfer at the microscale, thus obtaining nanocrystalline products with a smaller particle size and narrower distribution [5]. Patel et al.'s research points to another path. They found that methods such as wet grinding and high-pressure homogenization do not use organic solvents in the entire preparation process, which fundamentally avoids the problem of solvent residue; It does not require the drug to have the property of dissolving in organic solvents. Because of their stronger universality, these two methods have now become the preferred solutions for industrial production of nanocrystals [1].

2.2. Top-down techniques

The top-down approach refers to the comminution of large drug particles to the nanoscale using mechanical force. Due to the absence of organic solvents and strong process controllability, this approach is currently the mainstream choice for industrial production [6]. The top-down approach mainly includes media milling and high-pressure homogenization. Most oral nanocrystal

formulations are produced using media milling (e.g., bead milling technology). The physical principle of this method is to reduce particle size through the impact, shear, and friction of milling beads, offering advantages such as simple processing, wide applicability, and suitability for large-scale manufacturing [7].

Banappa et al. found that in media milling, the crude drug powder is dispersed with suitable stabilizers in an aqueous or non-aqueous medium, together with milling media (such as glass beads, zirconium oxide beads, or cross-linked polystyrene beads), inside a milling chamber. Particle size reduction is achieved by the mechanical shear and impact forces generated by a high-speed rotor [7]. This process can be operated in either batch mode or continuous circulation mode, with the continuous mode being more favorable for producing consistent nanocrystals with small dimensions [7]. Meanwhile, this method also has risks such as long processing time, media residue, and microbial contamination. High-pressure homogenization (e.g., microfluidization) uses the shear, cavitation, and collision effects generated when a high-pressure fluid passes through a narrow gap to disintegrate the drug particles. It is divided into two types: piston-gap homogenization and microfluidization [8]. Kulkarni et al. found that in a piston-gap homogenizer, the drug suspension is forced by a piston through a narrow gap (about 5 μm), where particle size reduction is achieved by high shear forces, turbulence, and cavitation effects. In microfluidization technology, based on the jet stream principle, two fluid streams collide at high pressure in a Yshaped or Zshaped chamber, and particle rupture occurs through particleparticle collisions [8]. Compared with the media milling, this method has no residual organic solvents, small inter-batch differences, and high efficiency, but requires high equipment and energy consumption [7, 8].

3. Delivery application of drug nanocrystals

3.1. Oral delivery

The core principle of nanocrystal technology is to increase the saturation solubility and dissolution rate of poorly water-soluble drugs, thereby improving their oral bioavailability. In Macedo et al.'s review, it was mentioned that the oral bioavailability of originally insoluble anti-tumor drugs often significantly increases after being made into nanocrystals. For example, the AUC_{0-t} value of nintedanib nanocrystals in rats is 2.5 times higher than that of drug solutions dissolved in Tween [2]. The C_{max} and $\text{AUC}_{0-24\text{h}}$ of entrutinib nanocrystals increased by 4 times and 3 times, respectively, and eliminated the influence of food on absorption, maintaining the drug's in vivo exposure at the same level on an empty stomach and in a fed state [2]; The C_{max} and $\text{AUC}_{0-24\text{h}}$ of nilotinib nanocrystals increased by 1.5 times respectively, while the $\text{AUC}_{0-48\text{h}}$ of cyclosporin A nanocrystals showed a clear dose-dependent growth curve with decreasing particle size, which further confirms the key role of controlling particle size in oral absorption from another perspective [2]. Overall, Macedo et al.'s study not only confirmed the effectiveness of nanocrystal technology in enhancing oral absorption of poorly soluble drugs with solid pharmacokinetic data, but also provided a systematic theoretical guidance and valuable research inspiration for the optimization design of nanocrystal formulations from the perspectives of particle size regulation, elimination of food effects, and differentiation of dissolution and permeation mechanisms.

In addition, modifying the surface of nanocrystals can further regulate their absorption behavior in the intestinal environment. For example, coating nanocrystals with highly adhesive polymers such as chitosan can enhance the electrostatic interaction between the nanocrystals and the intestinal mucus layer, thereby prolonging their retention time in the intestine and increasing the concentration of drugs at the absorption site [2, 9]. Lin et al.'s study showed that chitosan heparin composite

nanoparticles can maintain fluorescence signals in the stomach for more than 6 hours after oral administration, and after fucose modification, their clearance effect on *Helicobacter pylori* is about 4 times higher than that of free drugs [2, 9]. If polyethylene glycol is used for modification, it can endow nanocrystals with the ability to penetrate mucus, allowing them to quickly pass through the mucus barrier and spread more evenly on the surface of intestinal epithelium [9]. If polyethylene glycol is used for modification, it can endow nanocrystals with the ability to penetrate mucus, allowing them to quickly pass through the mucus barrier and spread more evenly on the surface of intestinal epithelium [9]. After oral administration of PLA-PEG nanoparticles modified with Fc fragments, blood glucose levels were significantly reduced and maintained for 10 hours, while the unmodified group showed almost no hypoglycemic effect [9]. After oral administration of itraconazole nanocrystals crosslinked with agglutinin (WGA), C_{max} and AUC increased by about 3 times compared to unmodified nanocrystals, and were also 2 times higher than the non-crosslinked modified group [9]. The above strategies have demonstrated the enormous potential of nanocrystal platforms in the delivery of orally insoluble drugs.

3.2. Injection delivery

Injection delivery is another important application direction of nanocrystals. In the scenario of intravenous injection, nanocrystals, as a pure drug system without additional carriers, can achieve drug loading rates close to 100%. The direct benefit of this feature is that it can significantly reduce or even completely avoid solvents such as polyoxyethylene castor oil or Tween, which can cause serious side effects such as allergic reactions and nephrotoxicity caused by organic solvents or surfactants. As a result, medication risks are naturally reduced, and medication safety is more reliably guaranteed [10].

In addition, Patel et al.'s study also revealed that nanocrystals can passively target solid tumors with densely distributed blood vessels by enhancing the osmotic retention effect, which opens up a new delivery approach for anti-tumor drugs [1]. For example, in a glioma mouse model, the AUC (area under the drug time curve, which reflects the total exposure of the drug in the blood and is a key pharmacokinetic parameter for measuring drug absorption) of docetaxel nanocrystals coated on red blood cell membranes is 8.6 to 10.1 times higher than that of free drugs, and the half-life is also extended by 3.9 to 6.0 times, greatly enhancing the delivery efficiency of the drug to the brain [1]. The IC₅₀ value of paclitaxel nanocrystals modified with folic acid in liver cancer cells (the half maximal inhibitory concentration, which refers to the drug concentration required to inhibit 50% of tumor cell growth, and a lower value usually indicates stronger anti-tumor activity) was reduced by about 17 times compared to free drugs, and the tumor volume also significantly decreased, which strongly confirms its good tumor targeting ability [1].

For long-acting injections, nanocrystal technology has been successfully applied to several drugs, forming a drug depot after intramuscular injection to achieve sustained release over weeks to months [3]. For example, Rossier et al. reported that the long-acting formulation of paliperidone palmitate nanocrystals (Invega) can provide dosing intervals of 1 month (Sustenna) to 4 months (Trinza) by adjusting particle size and concentration [10]. The recently approved cabotegravir/rilpivirine nanocrystal combination (Cabenuva), as the first long-acting injectable for HIV, maintains viral suppression with once-monthly dosing and significantly improves patient adherence [3]. Overall, injection delivery has significant advantages in the delivery strategy of drug nanocrystals.

3.3. Localized and targeted delivery

The significant advantage of nanocrystals in topical delivery is mainly reflected in enhancing dermal drug penetration. Nanocrystals improve the saturation solubility and dissolution rate of poorly water-soluble drugs, creating a high concentration gradient between the skin and the formulation, thereby enhancing passive diffusion [3]. Their nanoscale size allows them to penetrate deeply into skin appendages such as hair follicles, while their high surface energy enhances bioadhesion, prolongs drug retention time on the skin surface, and forms a drug reservoir for sustained release [3].

Alnaim et al. found that diclofenac sodium nanocrystals showed better skin penetration and deposition than commercial formulations and coarse suspensions [3]. Luliconazole nanocrystals had a 5fold increase in solubility and a 4fold increase in dissolution rate, and showed better antifungal activity than conventional formulations [3]. Acyclovir nanocrystals had a 1.6fold higher saturation solubility than the micronized form; the skin permeation of the nanocrystal suspension and the nanocream was 6.3fold and 2.4fold higher, respectively, than that of conventional preparations [3]. Beclomethasone nanocrystals had a 745.5fold higher saturation solubility than the pure drug, and the local skin accumulation efficiency was significantly higher than that of the brand formulation [3]. It can be seen that after various drugs are formulated into nanocrystals, their skin penetration ability and local bioavailability are significantly improved, showing better efficacy than conventional formulations in the treatment of skin disorders such as inflammation, fungal infections, psoriasis, and herpes simplex virus infections. This delivery strategy can significantly enhance the dermal delivery efficiency of poorly water-soluble drugs, providing a more advantageous approach for the treatment of skin diseases.

4. Stability and safety challenges of nanocrystals

4.1. Stability issues of nanocrystals

The stability issue of nanocrystals usually needs to be viewed separately from the physical and chemical dimensions. In terms of physical stability, the main challenges come from aggregation phenomena and Ostwald ripening. The root cause of aggregation lies in the high surface energy of nanocrystals, which makes it easy for particles to merge with each other; Ostwald ripening describes the process of small particles continuously dissolving and large particles taking advantage of the opportunity to grow, which makes the particle size of the system increasingly uneven. To suppress these two trends, stabilizers are basically needed: ionic stabilizers such as chitosan and SLS rely on electrostatic repulsion to maintain the distance between particles; non-ionic stabilizers such as HPMC and F127 rely on steric hindrance to form a protective film around the particles, preventing their aggregation [2].

In terms of chemical stability, nanocrystals mainly face two major challenges: drug degradation and crystal transformation. Drug degradation is easy to understand, as many drugs are prone to hydrolysis or oxidation in aqueous media. Therefore, using non-aqueous solvent systems (such as glycerol-water systems) instead of traditional aqueous solvents to prepare nanocrystals can often effectively bypass this problem. As for the transformation of crystal structure, the process of nanomaterialization itself may cause drugs to transform from their originally ordered crystalline state to a disordered amorphous state, and even undergo polycrystalline transformation. Once this change occurs, it will have practical effects on solubility and system stability [6].

4.2. Challenges and prospects

Although the preparation technology of nanocrystals has become increasingly mature, it still faces the challenge of controlling particle size uniformity, crystal stability, and inter-batch reproducibility in large-scale production. At the same time, during long-term storage, nanocrystalline formulations are inevitably prone to stability issues such as sedimentation, aggregation, and continued crystal growth, which can affect product quality and final efficacy [10]. Furthermore, the pollution risk caused by residual organic solvents and metal debris in the production process, as well as the stability and reproducibility of large-scale production itself, remain the main obstacles facing clinical translation [10].

Looking ahead, it still needs to leverage process analysis technology and the concept of quality-based design to gradually build and improve the online monitoring system, to more effectively promote the landing of nanocrystalline products in the industrial field. Overall, nanocrystals have become an important platform in the fields of oral, injection, and local delivery due to their high drug loading capacity, significant improvement in the bioavailability of poorly soluble drugs, and flexible adaptation to different routes of administration. Nanotechnology and drug delivery systems are still developing and have the potential to address current limitations such as poor solubility, low bioavailability, and non-specific distribution [1]. Emerging production technologies such as microfluidics and continuous manufacturing will also enhance the scale production capacity and control accuracy of nanocrystalline formulations, making the drug delivery process more consistent and efficient [1]. It can be foreseen that in the era of precision therapy, the value that drug nanocrystals can play will become even greater.

5. Conclusion

The bottom-up method is difficult to control due to the mixing process, which can easily lead to uneven particle size and batch differences, and is difficult to overcome the problem of residual organic solvents; In contrast, the top-down method simply does not use organic solvents, has stronger universality, and is easier to achieve precise control of the process, thus becoming the mainstream choice for industrial production at present. Based on these preparation strategies, nanocrystals have effectively improved the bioavailability of oral drugs by enhancing the dissolution rate and saturation solubility of poorly soluble drugs, and can achieve intestinal targeting, mucus penetration, and long-term sustained release through surface modification; During injection delivery, it cleverly avoids the toxicity issues of solubilizers and achieves tumor targeting; During local delivery, it greatly enhances its ability to penetrate the skin by creating a high concentration gradient.

However, the challenges faced by nanocrystals in terms of stability remain severe. The issue of physical stability still relies on ionic or non-ionic stabilizers; The challenge of chemical stability needs to be avoided by using non-aqueous solvent systems and optimizing preparation processes. So, choosing the right stabilizer and adjusting the preparation process are the key factors determining whether the nanocrystalline formulation can ultimately be stabilized. With the continuous deepening of research on drug nanocrystals, this technology is developing towards smarter and more diverse functions, which may provide some new intervention strategies for difficult-to-treat diseases.

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